A Black Buffalo Novel Nicotine Pouch Product is Bioequivalent to 4 mg Nicorette Gum

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Poster #19

Abstract

Black Buffalo Inc. (BB) has developed a pouch form of a novel smokeless alternative product that is based on a proprietary common non-tobacco food plant. The plant leaf is cured and processed like tobacco. Tobacco-derived nicotine is added in liquid form to the processed leaf. Black Buffalo's pouch product is designed to emulate the organoleptic, ritualistic, and pharmacokinetic aspects of traditional smokeless pouch products. The pharmacokinetics of nicotine absorption from Black Buffalo Wintergreen Pouch (BBWP) product was assessed and compared to 4 mg Nicorette® White Ice Mint gum. A randomized, open label, crossover, in-patient clinical study was performed in 28 subjects to evaluate the nicotine plasma levels. Subjects used one pouch of BBWP product or one piece of Nicorette gum under controlled conditions. Blood was collected for up to 180 minutes. The BBWP-associated plasma nicotine area under the curve (AUC) was 723 ng*min/mL and the AUC for Nicorette gum was 765 ng*min/mL. A bioequivalence calculation was performed on the AUC and it was found that the 90% confidence interval for the geometric means ratio lies within 80.00-125.00% indicating that BBWP is bioequivalent to 4 mg Nicorette gum, as per Health Canada Natural and Non-prescription Health Products Directorate.

The Product

Black Buffalo's tobacco alternative products were developed as an alternative to traditional moist smokeless tobacco (MST) products, with the intent of eliminating user exposure to the TSNAs and PAHs found in MST products. BB's products are made by applying food-grade flavors, pharmaceutical-grade tobacco-derived nicotine, salt, water, preservatives, humectants, and pH modifiers to a leafy vegetable food that has been flue-cured (i.e., dried using indirect heat), cut, and processed into a low-moisture biomass that resembles finely shredded tobacco. The biomass is enclosed in a fleece pouch material similar to traditional tobacco snus products (**Figure 1**).

The product does not contain any tobacco leaf or tobacco stem material, but it does contain tobacco-derived nicotine and is intended to emulate the organoleptic, ritualistic, and pharmacokinetic aspects of traditional MST products. The product is intended to be placed in the mouth between the cheek and gum for a period of time determined by the user (typically 30 to 60 minutes).

Figure 1. Black Buffalo Pouch Product

Methods

This was a randomized, open-label, crossover study designed to evaluate the nicotine pharmacokinetics (PK) of Black Buffalo Wintergreen Pouch compared to Nicorette 4 mg nicotine polacrilex gum in healthy adult male and female smokers who have experience using smokeless products.

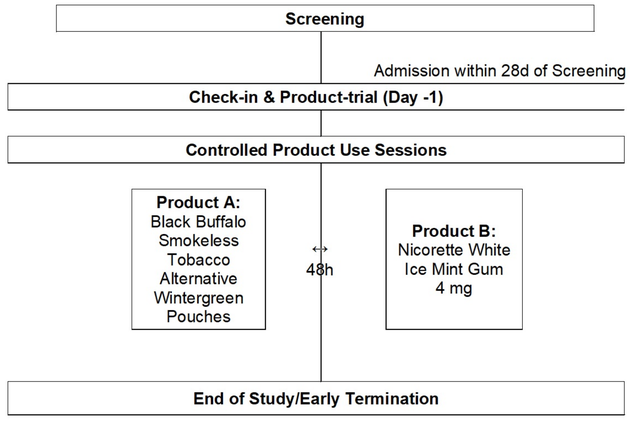
Subjects had to have a history of smoking an average of ≥10 cigarettes daily for at least 1 year. Subjects must have used a mint-flavored, smokeless tobacco product at least 20 times in their lifetime and at least once in the past 30 days (prior to study start). Subjects must have tested positive for urine cotinine (≥200 ng/mL) at Screening.

Subjects participated in a Standard Screening visit and a Confined Assessment Phase, which included a Product Trial Session on Day -1 and Product Use Session, which consisted of morning Controlled Product Use Sessions. Each study day of product use was separated by approximately 48 hours. Subjects chewed one piece of nicotine gum (chew and park method for 30 minutes) or placed the pouch in their mouth between the cheek and gum for 30 minutes. Blood sampling was within 5 minutes of start of product use (T0) and at 2, 5, 10, 15, 30, 45, 60, 90 and 180 minutes after product administration.

Study Design

Figure 2 shows the study design. The Bioequivalence analysis was conducted with linear mixed models in SAS 9.4® using the MIXED procedure. This statistical technique is used to account for the repeated measures resulting from the study's crossover design. For these models, the study subject was specified as the random effect, with the final model being characterized as a random effects mixed model. The outcomes for the analysis were Area Under the Curve (AUC) for T0 to the last quantifiable concentration (AUC0-t) and times 0-180 minutes (AUC0-180). Bioequivalence was concluded if the 90% confidence interval of the AUC ratio of geometric least squared means was entirely within the range of 80%-125%. This range for evaluation is standard in pharmacokinetic bioequivalence studies.

Figure 2. Study Design



Results

A total of 28 subjects were randomized and 25 completed the study. All subjects reported smoking approximately one pack of cigarettes a day and had been smoking for approximately 20 years.

Nicotine plasma levels were measured after controlled use of the products. The Black Buffalo Wintergreen pouch product contained 9.5 mg of nicotine and the Nicorette® White Ice Mint gum was labeled 4 mg.

Figure 3 shows the baseline adjusted plasma nicotine concentrations of each product and **Table 1** shows the derived Nicotine parameters. The Black Buffalo product has nicotine applied to the plant material whereas the Nicorette gum is made with nicotine polacrilex. The nicotine polacrilex complex is intended to control the release of nicotine. The nicotine absorption from the Black Buffalo Pouch product was slightly faster (Tmax = 35 minutes vs 44 minutes for the gum). The exact Tmax is unknown due to the selection of the sampling time points. The maximum amount of nicotine absorbed (Cmax) was similar for the two products with a mean of 7.1 ± 3.2 ng/ml for the Black Buffalo Pouch product and 6.6 ± 3.1 ng/ml for the Nicorette gum. The AUC after 180 minutes for the products was very similar (724 ng*min/ml for Black Buffalo Pouch and 765 ng*min/ml for the Nicorette gum).

The bioequivalence (BE) analysis (**Table 2**) showed that the Black Buffalo Pouch was bioequivalent to the Nicorette gum for both the AUC0-t and the AUC0-180. The point estimate and 90% CI for the AUC0-t ratio of geometric least squared means was 102.13 (87.39 – 119.35) and fell entirely within the 80%-125% range; indicating BE between these two products. Results for AUC0-180 were similar, as the ratio of geometric least squared means was 97.71 (83.37, 114.53) and also was completely within the range of bioequivalence.

Results

Figure 3. Baseline Adjusted Plasma Nicotine Concentrations

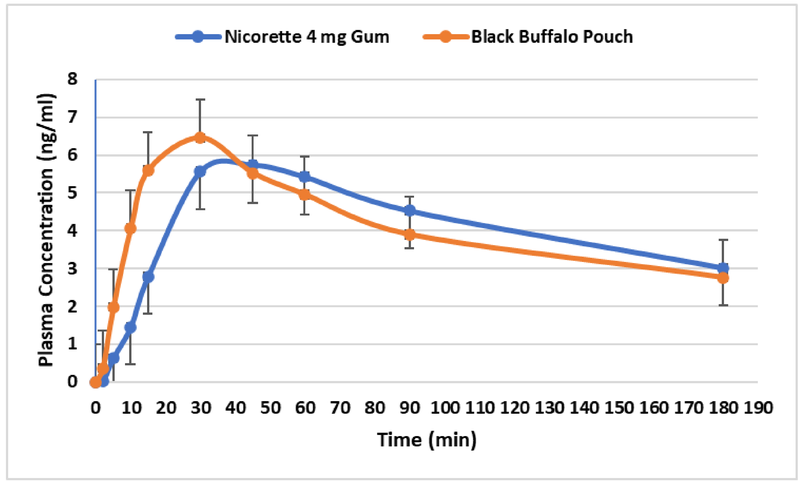


Table 1. Nicotine Pharmacokinetic Parameters

Parameter	Black Buffalo Wintergreen Pouch	Nicorette Gum 4 mg
C_{max} (ng/mL)	n=28	n = 27
Mean (SD)	7.069 (3.181)	6.607 (3.118)
T_{max} (minutes)	n=28	n=27
Median	30.06	45.00
AUC_{0-180} (ng*min/mL)	n=25	n=20
Mean (SD)	**723.902** (251.342)	**765.114** (331.536)
AUC_{0-t} (ng*min/mL)	n=28	n=27
Mean (SD)	**731.829** (300.551)	**724.984** (308.650)

Table 2. Bioequivalence Parameters

Parameter	Black Buffalo Wintergreen Pouch	Nicorette Gum 4 mg	Geometric Least Squared Mean Ratio	90% Confidence Interval
AUC_{0-180} (ng*min/mL)	n=25	n=20	-	-
Geometric Mean (SD)	703.259	661.653	**97.71**	**83.37 – 114.53**
AUC_{0-t} (ng*min/mL)	n=28	n=27	-	-
Geometric Mean	669.173	673.766	**102.13**	**87.39 - 119.35**

Conclusions

The Black Buffalo Pouch product is designed to emulate the organoleptic, ritualistic, and pharmacokinetic aspects of traditional smokeless pouch products. Black Buffalo makes no smoking cessation claims about the product in the United States. **The analysis presented here indicates that the product is bioequivalent to Nicorette 4 mg nicotine gum, an FDA approved nicotine replacement therapy.**

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